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WASHINGTON, D.C. 20036

In re Application of
SCHROEDER, Hartwig
Serial No: 09/622,419
Filed: August 16, 2000
Attorney Docket No: 48792

: Petition to Review Lack of Unity
:Under 37 C.F.R. 1.144

This is in response to applicants petition under 37 CFR 1.144, filed December 2, 2003, requesting review of the Examiner's lack of unity requirement mailed February 12, 2003. The delay in acting on this petition is regretted.

BACKGROUND

This application is a US national stage application properly filed under 35 USC 371.

The Examiner instituted a lack of unity requirement of claims 1-14 into seven different Groups in an office action mailed February 12, 2003 as follows:

Group I, claims 1-6 & 12, in part, drawn to a process of producing biotin using a host organism transformed with gene SEQ ID No 1 [S-adenosylmethionine synthase gene] and SEQ ID No 3 [bioS1];

Group II, claims 1-6 & 12, in part, drawn to a process of producing biotin using a host organism transformed with gene SEQ ID No 1 and SEQ ID No 5 [bioS2];

Group III, claims 1-6 & 12, in part, drawn to a process of producing biotin using a host organism transformed with gene SEQ ID No 1 and SEQ ID No 7 [bioS3];

Group IV, claims 7-11 & 14, in part, drawn to a gene construct comprising gene SEQ ID No 1 and SEQ ID No 3 [bioS1];

Group V, claims 7-11 & 14, in part, drawn to a gene construct comprising gene SEQ ID No 1 and SEQ ID No 5 [bioS2];

Group VI, claims 7-11 & 14, in part, drawn to a gene construct comprising gene SEQ ID No 1 and SEQ ID No. 7 [bioS3];

Group VII, claim 13, drawn to a "use" of gene SEQ ID No 7 [bioS3] alone or in combination with S-adenosylmethionine synthase gene and/or bioS1/S2/A/B/F/C/D/H/P/W/X/Y/R to produce biotin.

Applicant elected Group I, with traverse, which was not found persuasive by the Examiner; and the lack of unity was subsequently made final.

Applicant additionally added a new claim 15 drawn to a method for producing biotin by expressing (e.g. procaryote or eucaryote) a gene comprising SEQ ID No 1, and at least one biotin synthesis gene selected from the group consisting of O-acetylserine sulfohydrolase A, O-acetylserine sulfohydrolase B, beta-cystathionase, nifS, and their procaryotic and eucaryotic homologues.

RELEVANT AUTHORITY

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding technical features. See Annex B: Unity of Invention, Part 1 "Instructions Concerning Unity of Invention"MPEP AI-63 (Rev. 1. Feb. 2003). An international or a national stage application are considered to have unity of invention where there exists a "special technical feature" that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. See PCT Rule 13.2; 37 CFR 1.475(a), (b)(1) and (2).

Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims and

(i) If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims;
(ii) If however, an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on the claim need to be carefully considered. If there is no link remaining an objection of lack of unity a posteriori (that is, arising only after assessment of the prior art) may be raised. See ANNEX B: Unity of Invention Part 1 "Instructions Concerning Unity of Invention" MPEP AI-6 (Rev. 1. Feb. 2003).

DISCUSSION

Original claims 1, 7 , 13 and newly added claim 15 are illustrative:

1. A process for producing biotin wherein an S-adenosyl methionine synthase gene, having the sequence SEQ ID No 1 and at least one further biotin syntheses gene bioS1, bioS2 or bioS3, having the sequences SEQ ID No 3, SEQ ID No 5 or SEQ ID No 7, and also their functional variants, analogues or derivatives, are expressed in a procaryotic or eucarytoic host organism which is able to synthesize

biotin, this organism is cultured and the synthesized biotin is used directly after separating off the biomass or after purifying the biotin.

7. A gene construct which comprises an S-adenosyl methionine synthase gene, having the sequence SEQ ID No 1 and at least one further biotin syntheses gene bioS1, bioS2 or bioS3, having the sequences SEQ ID No 3, SEQ ID No 5 or SEQ ID No 7, and also their functional variants, analogues or derivatives, and which is functionally linked to one or more regulatory signals for the purpose of increasing gene expression and/or protein expression and/or whose natural regulation has been switched off.

13. The use of the bioS3 gene, having the sequence SEQ ID No 7, or of its functional variants, analogues or derivatives, either alone or in combination with at least one further gene selected from the group S-adenosylmethionine synthase gene, bioS1, bioS2, bioA, bioB, bioF, bioC, bioD, bioH, bioP, bioW, bioX, bioY or bioR, for producing biotin.

15. A process for producing biotin wherein an S-adenosylmethionine synthase gene having the sequnece SEQ ID No 1, and at least one biotin biosynthesis gene selected from the group consisting of O-acetylserine sufohydrolase A, O-acetylserine sulfohydrolase B, beta-cystathionase, nifS, and their prokaryotic eucaryotic homologues, are expressed in a prokaryotic or eukaryotic host organism which is able to synthesize biotin, this organism is cultured and the synthesized biotin is used directly after separating off the biomass or after purifying the biotin.

Applicant argues that Groups I-VI possess unity of invention based on SEQ ID No 1 being a "special technical feature" which is present with each of the different biotin syntheses genes (SEQ ID No 3, 5 or 7) in the genetic construct combinations present in each of Groups I-VI.

Applicant additionally argues, that in accordance with PCT Rule 13 and 37 CFR Section 1.475, unity of invention exists between Groups (I and IV), Groups (II and V) and Groups (III and VI), since the corresponding genetic constructs are necessary for use in a method utilizing the same genetic constructs in order to successfully transform a host organism to produce biotin. For example, the Group IV gene construct comprising SEQ ID No 1 and SEQ ID No 3 is a common technical feature with Group 1 which utilizes the same genetic construct for producing biotin.

Applicant's arguments were considered but deemed nonpersuasive for the following reasons.

Applicant is correct that the method Groups I-III and the product Groups IV-VI share a technical feature of SEQ ID No 1, however PCT Rule 13.2 requires that the technical feature make a contribution over the prior art in order for unity of invention to exist. In this application, the technical feature of SEQ ID No 1 does not make contribution over the prior art. The Search Report for the parent PCT/EP99/01052 cites Patent Abstract of Japan Vol. 098, No. 001 (Jan. 30,

1998) which teaches genetically-engineered production of biotin using a recombinant plasmid containing the SAM-synthase gene (e.g. SEQ ID No 1).

Additionally, although the applicant is correct that the gene construct comprising SEQ ID No 1 and a biosyntheses gene (e.g. SEQ ID No 3, 5 or 7) is a common technical feature, it does not serve to link its corresponding method of use since it is not a "special" technical feature. The biosyntheses gene as broadly claimed further includes " functional variants, analogues or derivatives" which do not make a contribution over the prior art. This is illustrated by the Patent Abstract of Japan Vol. 098, No. 001 (Jan. 30, 1998) which teaches genetically-engineered production of biotin using a recombinant plasmid containing the SAM-synthase gene (e.g. SEQ ID No 1) and the biotin operon which must include a biosyntheses gene representative of "functional variants, analogue or derivative" of any of SEQ ID No 3, 5 or 7. It is further noted in this regard, that biosyntheses genes of SEQ ID No 3, 5 and 7 and "functional variants, analogue or derivative" do not themselves represent a special technical feature. See e.g. present specification page 2, lines 25-35 (describing bioB, bioS1 and bio S2 genes for stimulating biotin syntheses); and Database EMBL, Accession No: F65063 12.09.1997 (bioS1), Database SWISSPROT, Accession No.: P39171 10.02.1995 (bioS2), and Database EMBL, Accession No. H64925 12.09.1997 (bioS3) cited in the Search Report.

Moreover, Applicant's arguments for the rejoinder of the product groups with the methods groups are not persuasive. Groups IV, V and VII are processes of using the products of Groups I, II and III. As such, these pairs of inventions are characterized as different categories of invention. If the elected method invention and it corresponding product invention are found to make a contribution over the prior art, the lack of unity determination between those two groups will be withdrawn. Because there is prior art on the method invention, the request for rejoinder of Groups (II and V) and Groups (III and VI) is not persuasive at this time.

With regard to Group VII (claim 13 above), Applicant asserts that "[T] he improved biotin syntheses achieved by this process is a special technical feature shared with the claims in groups I-VI." This argument was considered, but deemed not persuasive for the following reasons.

Initially, it is noted that claim 13 is a nonstatutory "use" claim and thus is unclear as to whether a composition or a process (as asserted by applicant) is intended.

In any event, claim 13 encompasses the "use" of SEQ ID No 7 (or its functional variants, analogues or derivatives) *alone* or in combinations with SEQ ID No 1 or additionally with one or more synthase genes. Thus Claim 13 does not require the SEQ ID No. 1, nor does it require any of the combinations set forth in Groups I-VI.

Furthermore, as pointed out above, neither SEQ ID No 7 (bioS3) nor its "functional variants, analogues or derivatives" or their use to produce biotin represent a special technical feature in light of the prior art of record cited in the specification as well as in the PCT/EP99/01052 Search Report teaching SEQ ID No 7 or other synthase genes which would represent " functional variants, analogues or derivatives" of SEQ ID No 7 used to produce biotin. See e.g. present specification page 2, lines 25-35 (describing bioB, bioS1 and bio S2 genes for stimulating biotin syntheses); and Database EMBL, Accession No: F65063 12.09.1997 (bioS1), Database

SWISSPROT, Accession No.: P39171 10.02.1995 (bioS2), Database EMBL, Accession No. H64925 12.09.1997 (bioS3) and Patent Abstract of Japan Vol. 098, No. 001 30.01.1998 ("functional variant, analog or derivative" of SEQ ID No 7 to produce biotin) cited in the Search Report.

Thus the Examiner was correct to withdraw newly submitted claim 15 from examination (e.g. see office action mailed 10/07/03 page 2) because this claim lacks unity of invention in view of the discussion above regarding the failure of SEQ ID No 1 to constitute a special technical feature. Additionally, claim 15 does not encompass the elected subject matter of SEQ ID No 1 and SEQ ID No 3 (bioS1) to which applicant has already received an action on the merits.

DECISION

Applicant's petition is **DENIED** for the reasons recited above.

Any request for consideration must be filed within two (2) months of the mailing date of this decision.

Upon reconsideration, the finality of the office action dated October 7, 2003 has been withdrawn. The application will be forwarded to the Examiner for the preparation of a Supplemental Office action consistent with this decision including:

a. the applicability of references cited in the PCT/EP99/01052 Search Report, particularly Patent Abstract of Japan Vol. 098, No. 001 (Jan. 30, 1998); and

b. reconsideration of the indication of allowable subject matter concerning SEQ ID No 1 and SEQ ID No 3 and if deemed allowable, reasons for allowance provided.

Should there be any questions regarding this decision, please contact Julie Burke, Special Program Examiner, by mail addressed to Director, Technology Center 1600, PO BOX 1450, ALEXANDRIA, VA 22313-1450, or by telephone at (571) 272-0512 or by facsimile transmission at (571) 305-7230.

Bruce Kisliuk
Director, Technology Center 1600

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,419	08/16/2000	Hartwig Schroder	48792	3392

26474 7590 05/14/2003

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WASHINGTON, DC 20036

EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	7

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/622419	Schroder et al	
Examiner	Group Art Unit	
T. Saidha	1652	7

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3/13/03 (Election).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above claim(s) II-VII (Claims) are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-6 & 12 (SEQ ID NOS: 1 & 3) is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-14 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. The Preliminary Amendment and request for reconsideration of the restriction requirement, filed 3.13.03 (Paper No. 6) is acknowledged.

2. ***Election***

Lack of Unity of Invention.

Applicant's election with traverse of Group I, claims 1-6 and 14 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that each of the defined groups other than group VII, contain reference to a combination of S-adenosylmethionine synthase (SAM-synthase) and one of the three identified biotin synthesis genes (bioS1, bioS2 and bioS3). Co-expression of the SAM-synthase gene with one or more of the biotin synthesis genes is a technical feature defining a contribution which each invention, considered as a whole, makes over the prior art.

Applicant's argument is considered and found not persuasive because each combination of SAM-synthase and a biotin synthesis gene as defined by the claim is considered independent and distinct and do not share the same technical feature among the groups. For example the coexpression of SAM-synthase and **bioS1** for biotin production is distinct from the coexpression of SAM-synthase and **bioS2** or coexpression of SAM-synthase and **bioS3**, because in each of these combinations, the structures or activities induced due to presence of bioS1, bioS2 and bioS3 in the gene construct are distinct from one another and therefore not shared among the various groups.

The lack of unity determination is still deemed proper under the PCT treaty and is therefore made FINAL.

3. Claims 1-6 & 12 (in-part) drawn to a process of producing biotin using a host organism transformed with the gene sequence of SEQ ID NO : 1 [SAM-synthase] and the biotin synthesis gene of SEQ ID NO : 3 [bioS1] are under consideration in this examination.

4. Claims corresponding to non-elected groups II-VII are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

5. Priority

Acknowledgment is made of applicants' claim for priority based on an application filed in Germany on 2.19.98.

6. ***Drawings***

Applicants drawing submitted in this application has been approved by the Draftsman.

7. Claims corresponding to groups II-VII are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

8. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Claim 12 provides for the use of sequences of claim 1 for biotin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

10. ***Enablement Rejection***

Claims 1-6 & 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, does not reasonably provide enablement for using any of the functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 (claims 1, 3-6 & 12), or wherein the deduced amino acid sequences of the gene sequences of SEQ ID NO : 1 & 3 have a homology of 30-100% and enable increased biotin production (claim 2), or express the variously modified sequences in various host organisms irrespective of the host being capable of producing biotin, or its expression in regulation-defective biotin mutants (claims 3-6), either alone or in shared vector or on separate vectors. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have described a single construct of co-expression of the combination of metk (SEQ ID NO : 1) and bioS1 (SEQ ID NO : 3) from *Escherichia coli* (see pages 15 of the instant specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims are so broad as to encompass a process of using a modified gene of SEQ ID Nos. 1 & 3 for biotin production, wherein the sequences are modified by any extent and includes deletion, substitution or insertion (functional variants); prokaryotic or eukaryotic homologues from bacteria, fungi, plant, animal or human (functional analogues)and truncated sequences thereof; or derivatives (claims 1, 3-6 & 12), or wherein the sequences are modified to having sequence homologies of 30-100% (claim 2) (*see* Specification, page 5, lines 22-47 for Applicants definitions). Applicants have neither disclosed nor described, or exemplified the numerous proposed modifications encompassed by the claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of SAM-synthase and/or biotin biosynthesis genes broadly encompassed by the process claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and

guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequences of SEQ ID Nos. 1 & 3 from which amino acid sequences can be deduced.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of SEQ ID Nos. 1 & 3 or that ranging in homology from 30-100% identity to the encoded amino acid sequences, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of enzyme to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any enzyme residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method or process of using said enzyme(s) with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of process of using such enzymes (SAM-synthase & biotin biosynthesis enzyme) having the desired biological characteristics or its co-expression into any host which may include a host cell not capable of biotin production, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

11. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1-6 & 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-6 & 12 recite 'functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3. However, description to any such functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 is lacking (claims 1-6 & 12).

Further claim 2, recite '30-100% homology to the deduced amino acid sequences of SEQ ID Nos. 1 & 3 The specification, however, only provides a process for using a single representative

species of a combination of full length gene sequences from *E. coli* of SEQ ID Nos. 1 & 3 for biotin production. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species or modify the enzyme by substitution, insertion or deletion (analogues, variants or derivatives) or make a polypeptide 30-99 % identical to the encoded amino acid sequences deduced from the gene sequences SEQ ID Nos. 1 & 3 and have desired biological activities for biotin production. The specification also fails to describe additional representative species of these combinations by way if modifications such as that claimed by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Further, description of expressing SEQ ID Nos. 1 & 3 into any prokaryotic or eukaryotic host organism either alone, or on shared vector or on separate vectors is also lacking. Given this lack of additional representative species, such as the proposed modifications of SEQ ID Nos. 1 & 3 and still retain functional characteristics of a process of producing biotin, or various host cells or the expression into single or shared vector, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

12. ***Claim Rejections - 35 U.S.C. § 112*** (second paragraph)

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, lines 1-4, recite 'claim 1' twice which is not required. Further claim 2, line 3-4, recite 'on the amino acid level deduced from the sequences ...'. The claim is confusing because it is not clearly stated or worded the relationship between the homology and the sequences. Rephrasing the claim to clarify the claim will overcome this rejection.

13. ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-4 & 12 are rejected under the judicially created doctrine of double patenting over claims 1-7 of U. S. Patent No. 6,436,681 (Schroder et al.) since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Claims are drawn to a process of producing biotin using SEQ ID Nos. 1 & 3 which have been modified to any extent by insertion, deletion or substitution [see Applicants' definition for functional

variants or analogs or derivatives, on page 5]. Such unlimited modifications to the sequences would result in sequences that will read on the process of producing biotin using SEQ ID Nos. 1 & 3 of the patent.

14. ***Allowable Subject matter*** (an example)

Claim 1 : A process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, culturing the host organism, separating off the biomass followed by purification and recovery of the biotin.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TSaidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
May 12, 2003

FINAL Rej

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,419	08/16/2000	Hartwig Schroder	48792	3392

26474 7590 10/07/2003

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WASHINGTON, DC 20036

EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	9

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/622419	Schroder
Examiner	**Group Art Unit**
T. Saidha	1652

9

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P ri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE -3- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- [X] Responsive to communication(s) filed on 8/18/03 (Paper #8).
- [X] This action is **FINAL.**
- [ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

- [X] Claim(s) 1 & 3-6 & 15 is/are pending in the application.
  - Of the above claim(s) 15 is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [X] Claim(s) 1 & 3-6 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- [X] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).
  - [X] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
  - [X] received.
  - [ ] received in Application No. (Series Code/Serial Number) _____.
  - [ ] received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

- [ ] Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- [ ] Interview Summary, PTO-413
- [ ] Notice of Reference(s) Cited, PTO-892
- [ ] Notice of Informal Patent Application, PTO-152
- [ ] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Other _____

Office Acti n Summary

1. Applicants' amendment and reply filed 8.18.02 (Paper No. 8) is acknowledged. Claims 1 & 3-6 are pending and under consideration in this examination.

2. Claim 15 is not being considered along with the processes claims because of the prior Lack of Unity of Invention, and according to which - Claims 1-6 & 12 (in-part) drawn to a process of producing biotin using a host organism transformed with the gene sequence of **SEQ ID NO : 1** [SAM-synthase] and the biotin synthesis gene of **SEQ ID NO : 3** [bioS1] were under consideration.

3. Applicants are reminded again that SEQ ID NO : 5 & 7 or similarly unrelated language is not under consideration, and that subject matter of inventions of Groups not under consideration be deleted, for example, current claims 1 & 3-6.

4. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

5. ***Enablement Rejection***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, does not reasonably provide enablement for using any of the functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 (claims 1, 3-6 & 12), or wherein the deduced amino acid sequences of the gene sequences of SEQ ID NO : 1 & 3 have a homology of 50-100% and enable increased biotin production, or express the variously modified sequences in various host organisms irrespective of

the host being capable of producing biotin, or its expression in regulation-defective biotin mutants (claims 3-6), either alone or in shared vector or on separate vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have described a single construct of co-expression of the combination of metk (SEQ ID NO : 1) and bioS1 (SEQ ID NO : 3) from *Escherichia coli* (see pages 15 of the instant specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims are so broad as to encompass a process of using a modified gene of SEQ ID Nos. 1 & 3 for biotin production, wherein the sequences are modified by any extent and includes deletion, substitution or insertion (functional variants or analogs); prokaryotic or eukaryotic homologs from bacteria, fungi, plant, animal or human (functional analogues)and truncated sequences thereof; or derivatives (claims 1, 3-6), or wherein the sequences are modified to having sequence homologies of 50-100% (claim 2) (*see* Specification, page 5, lines 22-47 for Applicants definitions). Applicants have neither disclosed nor described, or exemplified the numerous proposed modifications encompassed by the claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of SAM-synthase and/or biotin biosynthesis genes broadly encompassed by the process claims. Since the amino acid sequence of a protein

determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequences of SEQ ID Nos. 1 & 3 from which amino acid sequences can be deduced.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of SEQ ID Nos. 1 & 3 or that ranging in homology from 50-100% identity to the encoded amino acid sequences, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of enzyme to modification and extent of such tolerance; © a rational and predictable scheme for modifying any enzyme residues with an expectation of obtaining the desired biological

function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method or process of using said enzyme(s) with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of process of using such enzymes (SAM-synthase & biotin biosynthesis enzyme) having the desired biological characteristics or its co-expression into any host which may include a host cell not capable of biotin production, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants Arguments :

Applicants citing specification page 5, lines 23-29, argue that the specification clearly indicate that a number of other enzymes are known to have the ability to assume the enzymic activity of bioS1, bioS2 & bioS3. Given the broad range of genes known in the art to be suitable substitutes, the ability of one skill in the art to recognize and use functional equivalents is relatively high - accordingly the homology range now recited in claim 1 is enabled.

In response, first it is again emphasized that bioS1 or SEQ ID NO : 3 & SEQ ID NO : 1 is under consideration. Further, it is not clear what broad range of genes are known as suitable

substitutes. What substitutes are functional equivalents ? And how Applicants have arrived at the conclusion that the homology range of 50-100% is now enabled ? Clearly the specification provides no guidance to any enablement issues or written description issues as indicated by the Applicants. Applicants have clearly, either in-part or wholly not addressed many of the issues pertaining to enablement or written description rejections presented in the prior Office Action.

6. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1 & 3-6 recite 'functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3. However, description to any such functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 is lacking (claims 1 & 3-6).

Further claim 1, recite '50-100% homology to the deduced amino acid sequences of SEQ ID Nos. 1 & 3 The specification, however, only provides a process for using a single representative species of a combination of full length gene sequences from *E. coli* of SEQ ID Nos. 1 & 3 for biotin production. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species or modify the enzyme by substitution, insertion or deletion (analogues, variants or derivatives) or make a polypeptide 50-100 % identical to the encoded amino acid

sequences deduced from the gene sequences SEQ ID Nos. 1 & 3 and have desired biological activities for biotin production. The specification also fails to describe additional representative species of these combinations by way if modifications such as that claimed by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Further, description of expressing SEQ ID Nos. 1 & 3 into any prokaryotic or eukaryotic host organism either alone, or on shared vector or on separate vectors is also lacking. Given this lack of additional representative species, such as the proposed modifications of SEQ ID Nos. 1 & 3 and still retain functional characteristics of a process of producing biotin, or various host cells or the expression into single or shared vector, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicants Arguments : No specific arguments presented.

7. Double patenting rejection made in the prior Office action, being no more relevant to the amended claims, is hereby withdrawn.

8. ***Allowable Subject matter*** (an example)

Claim 1 : A process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, culturing the host organism, separating off the biomass followed by purification and recovery of the biotin.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T C Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
October 3, 2003

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,419	08/16/2000	Hartwig Schroder	48792	3392

26474 7590 02/12/2003

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EXAMINER
SAIDHA, TEKCHAND

ART UNIT	PAPER NUMBER
1652	5

DATE MAILED: 02/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/622419	Schroder et al	
Examiner	Group Art Unit	
T. Saidha	1652	5

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE One MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10/10/00 (105).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-14 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Acti n Summary

Lack of Unity of Invention

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-6 & 12 (In-part), drawn to a process of producing biotin using a host organism transformed with at least gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 3 [bioS1].

Group II, claim(s) 1-6 & 12 (In-part), drawn to a process of producing biotin using a host organism transformed with at least gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 5 [bioS2].

Group III, claim(s) 1-6 & 12 (In-part), drawn to a process of producing biotin using a host organism transformed with at least gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 7 [bioS3].

Group IV, claim(s) 7-11 & 14 (In-part), drawn to a gene construct comprising gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 3 [bioS1].

Group V, claim(s) 7-11 & 14 (In-part), drawn to a gene construct comprising gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 5 [bioS2].

Group VI, claim(s) 7-11 & 14 (In-part), drawn to a gene construct comprising gene sequences of SEQ ID NO : 1 [S-adenosylmethionine synthase gene] and SEQ ID NO : 7 [bioS3].

Group VII, claim(s) 13, use of gene sequence of SEQ ID NO : 7 [bioS3].

2. The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has a special technical feature of DNA sequences of SEQ ID NO : 1 & 3 used in transforming a host organism which Groups II-VII do not share; Group II has a special technical feature of DNA sequences of SEQ ID NO : 1 & 5 used in transforming a host organism which Groups I & III-VII do not share; Group III has a special technical feature of DNA sequences of SEQ ID NO : 1 & 7 used in transforming a host organism which Groups I-II & VI-VII do not share; Group IV has a special technical feature of a gene construct using DNA sequences of SEQ ID NO : 1 & 3 which Groups I-III & V-VII do not share; Group V has a special technical feature of a gene construct using DNA sequences of SEQ ID NO : 1 & 5 which Groups I-IV & VI-VII do not share; Group VI has a special technical feature of a gene construct using DNA sequences of SEQ ID NO : 1 & 7 which Groups I-V & VII do not share; Group VII has a special technical feature of using DNA sequences of SEQ ID NO : 3 which Groups I-VI do not share. Thus the various groups discussed show a lack of unity of invention.

3. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventor ship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventor ship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

5. ***Sequence Rules***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. See the enclosed notice to comply. Specifically, Rule 1.822(e) requires the use of three letter abbreviation for amino acids. See the enclosed notice to comply. Specifically, Rule 1.822(e) requires the use of three letter abbreviation for amino acids.

New Sequence Rules

Since the effective filing date after July 1, 1998, Applicants should follow the New Rule Format and submit a new Sequence Listing (both in electronic and paper format). Compliance according to the requirements of 37 CFR 1.821 through 1.825 is required.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T C Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
February 7, 2003